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The role of thyroid hormone nuclear receptors in the heart: evidence from pharmacological approaches

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Abstract This review evaluates the hypothesis that the cardiac effects of amiodarone can be explained—at least partly—by the induction of a local 'hypothyroid-like condition' in the heart. Evidence supporting the hypothesis comprises the observation that amiodarone exerts an inhibitory effect on the binding of T3 to thyroid hormone receptors (TR) alpha-1 and beta-1 in vitro, and on the expression of particular T3-dependent genes in vivo. In the heart, amiodarone decreases heart rate and alpha myosin heavy chain expression (mediated via TR alpha-1), and increases sarcoplasmic reticulum calcium-activated ATP-ase and beta myosin heavy chain expression (mediated via TR beta-1). Recent data show a significant similarity in expression profiles of 8,435 genes in the heart of hypothyroid and amiodarone-treated animals, although similarities do not always exist in transcripts of ion channel genes. Induction of a hypothyroid cardiac phenotype by amiodarone may be advantageous by decreasing energy demands and increasing energy availability.

Keywords Amiodarone · Dronedarone · Hypothyroidism · Thyroid hormone receptor alpha-1 · Thyroid hormone receptor beta-1 · Heart rate · Alpha MHC · Beta MHC · SERCA2a

Introduction

The heart is an important target organ for thyroid hormone as evident from clinical practice [1]. In hyperthyroid patients there is an increased resting heart rate, increased left ventricular contractility, increased cardiac output and a decreased systemic vascular resistance, resulting in a lower diastolic and higher systolic blood pressure; serum cholesterol is decreased and patients are susceptible to cardiac arrhythmias, specifically to atrial fibrilation. In contrast, hypothyroid patients have a decreased heart rate, impaired cardiac contractility and diastolic function, decreased cardiac output and an increased systemic vascular resistance, resulting in a higher diastolic blood pressure; serum cholesterol is increased and patients are susceptible to accelerated atherosclerosis and coronary artery disease. The aberrant cardiovascular functions in hyperthyroid and hypothyroid patients are usually fully reversible upon restoration of the euthyroid state.

Amiodarone, introduced originally as an anti-anginal agent but nowadays used as a very potent antiarrhytmic drug, lowers heart rate, lengthens the cardiac action potential (manifest as a longer QTc interval on the EKG), and depresses myocardial oxygen consumption [2]. In addition, amiodarone increases plasma cholesterol [3]. Similarities between the effects of amiodarone and of hypothyroidism are striking. It has therefore been hypothesized that the cardiac effects of amiodarone can be explained—at least partly—by the induction of a local 'hypothyroid-like' condition in the heart [3]. In this review we present evidence in favour of this hypothesis derived from experimental animal studies focussing on nuclear T3 receptors and thyroid hormone-dependent gene expression in the heart.

Hypothyroidism

Genomic effects of thyroid hormone in the heart are mediated via nuclear T3 receptors (TR). There are several

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isoforms of TRs: TRα1 and TRβ1 (which both bind the ligand T3) and TRα2 (which does not bind T3 but is able to bind to thyroid response elements (TRE) and may exert a dominant negative effect on gene expression). The heart is a predominantly TRα1 organ, although TRβ1 is also expressed albeit at a lower level. In rats made hypothyroid by adding 0.05% propylthiouracil to their drinking water for 2 weeks, we did not observe any changes in atrial or ventricular gene expression of the three TRs relative to controls, neither at the mRNA level nor at the protein level [4]. Other models, however, did show changes in the expression of particular TR isoforms in hypothyroid rats [5, 6]. The discrepancy can be explained by the more severe hypothyroidism in these earlier studies by using propylthiouracil for a longer period of time (six instead of our 2 weeks) or combining propylthiouracil with a low iodine diet [5, 6]. Because in our model cardiac TR levels are not affected by thyroid hormone deficiency, observed changes in the expression of T3-dependent genes in the hypothyroid heart are likely attributed to a low occupancy rate of TR with T3.

There are a number of T3-responsive genes in the heart encoding for proteins involved in cardiac contractility. Examples are the sarcoplasmic reticulum calcium-activated ATPase (SERCA2a) which is responsible for the calcium reuptake during the diastole and is activated by T3 [7], and the two myosin heavy chains α and β (αMHC and βMHC, respectively) which are myofibrillar proteins that make up the thick filament of the cardiac myocyte contractile apparatus. In rodents, transcription of αMHC is activated by T3, whereas transcription of βMHC is repressed by T3 [8, 9]. In our experimental model, hypothyroidism was associated with a downregulation of αMHC and an upregulation of βMHC (both at the mRNA and at the protein level) in atria and ventricles; SERCA2a was significantly downregulated in atria and ventricles [4]. The observed changes are in good agreement with previous reports in the literature [8–10]. Downregulation of αMHC (the fast myosin with higher ATPase activity) under simultaneous upregulation of βMHC (the slow myosin), together with the downregulation of SERCA2a explains to a certain extent the decreased cardiac contractility associated with hypothyroidism [1]. Modulation of αMHC transcription is linked to the TRα1 isoform, whereas transcription of βMHC and SERCA2a genes seems to be under control of TRβ1 [11].

Amiodarone

Amiodarone treatment (100 mg/kg/day orally for 2 weeks) influences cardiac TR mRNA expression [12]: TRα1 is decreased in the right atrium but increased in the left ventricular wall, TRα2 remains unchanged at these locations, and TRβ1 is decreased both in the right atrium and the left ventricular wall. The overall downregulation of TR by amiodarone is similar to the reported downregulation of TRα1 and TRβ1 in the post-infarcted rat heart, which shows a hypothyroid cardiac phenotype [13].

Amiodarone treatment also influenced thyroid hormone-dependent gene expression in our experimental rat model at the mRNA level [12]: SERCA2a was reduced in the right atrium, αMHC was reduced both in the right atrium and left ventricular apex, whereas βMHC was increased in the right atrium, left ventricular wall and apex. The findings are in good agreement with the literature [14].

The data strongly suggests that amiodarone induces a hypothyroid-like phenotype with regard to T3-dependent gene expression in the heart. To learn about the mechanism by which amiodarone exerts these effects, we performed a number of in vitro and in vivo studies. First, in vitro experiments demonstrated that amiodarone via its main metabolite desethylamiodarone (DEA) acts as a competitive inhibitor of T3 binding to TRα1 (IC50 value 30 $\pm$ 3.9 μM) and as a noncompetitive inhibitor of T3 binding to TRβ1 (IC50 value 71 $\pm$ 3.4 μM) [15, 16]. Next to inhibition of T3 binding to TR, DEA may further affect T3-dependent gene expression by inhibition of co-activator binding to TR and inhibition of the TR binding to TRE [17, 18]. Second, DEA concentrations in the rat heart after amiodarone treatment (100 mg/kg/day orally for 2 weeks) are in the micromolar range (14 μmol/kg) [19], close to the IC50 values of DEA for inhibiting T3 binding to TR in vitro. The T3 concentrations in rat heart are 4 times lower in amiodarone-treated animals than in control animals (1 vs 4 nmol/kg, respectively) [20]. The marked decrease in myocardial T3 concentration is related to the decrease of plasma T3 and the impaired entrance of plasma-derived T3 in hearts of amiodarone-treated animals [21]. The reduction of cardiac TR and T3 concentrations will result in all likelihood in a low occupancy of TR with T3, which favours the inhibitory effects of DEA [15, 16]. The finding that amiodarone modulates the gene expression of both αMHC (mediated via TRα1) and βMHC and SERCA2a (mediated via TRβ1) is in line with the inhibitory effect of DEA on the binding of T3 to both TRα1 and TRβ1.

Dronedarone

Dronedarone is a newly developed antiarrhythmic drug, structurally related to amiodarone. It lacks, however, the iodine moiety of amiodarone, and thereby iodine-related toxicity. Dronedarone like amiodarone has antiadrenergic effects as well as blocking effects on many ion channels. Dronedarone possesses rate-control and rhythm-control properties, and seems to be safe and effective in preventing

recurrence of atrial fibrillation [22]. We wondered if part of the pharmacological actions of dronedarone could also be attributed to induction of a local hypothyroid-like condition in the heart.

In vitro experiments demonstrate that debutyldronedarone (the major metabolite of dronedarone) inhibits the binding of T3 to TRα1 (IC50 value 59 $\pm$ 4.1 μM) much more strongly than the binding of T3 to TRβ1 (IC50 value 280 $\pm$ 29 μM) [23]. Inhibition of T3 binding to TRα1 by debutyldronedarone is competitive in nature. Treating rats with dronedarone (100 mg/kg/day orally for 2 weeks) decreases TRα1 mRNA in the right atrium, decreases TRβ1 mRNA in right atrium, left ventricular wall and apex, whereas it does not affect TRα2 mRNA in the heart [12]. With regard to T3-dependent gene expression, dronedarone did not change αMHC, βMHC and SERCA2a expression in the heart [12]. Pantos et al. [24] also did not observe a change in βMHC or SERCA2a cardiac expression in rats treated with dronedarone (90 mg/kg/d orally for 2 weeks), but did find a significant decrease in αMHC and heart rate. These findings are most interesting: the presence of an effect of dronedarone on heart rate and αMHC (both TRα1 mediated) and the absence of an effect of dronedarone on βMHC and SERCA2a (both TRβ1 mediated) reinforce the in vitro findings that dronedarone acts as a selective TRα1 antagonist. This has also been demonstrated in another rat study in which treatment with amiodarone reduced the expression of two TRβ1-dependent genes (as evident from a lower LDL receptor protein concentration and a lower iodothyronine-5′-deiodinase-activity in liver), whereas treatment with dronedarone did not [23].

Whether dronedarone like amiodarone also induces a local hypothyroid-like condition in the heart is less clear. However, further biochemical and functional studies showed many similarities in hearts of hypothyroid and dronedarone-treated rats, leading these authors to conclude that dronedarone treatment results in cardioprotection by selectively mimicking hypothyroidism [24].

Hypothyroid cardiac phenotype

Amiodarone treatment, like hypothyroidism, lowers heart rate, lenghthens the QTc interval, and lowers αMHC gene expression in the heart; these effects are TRα1-mediated effects. Amiodarone treatment, like hypothyroidism, increases βMHC and decreases SERCA2a gene expression in the heart; both effects are TRβ1-mediated effects. The data provides supportive evidence for the hypothesis that amiodarone induces a hypothyroid-like condition in the heart. Amiodarone apparently switches gene expression back into foetal programming of particular cardiac genes, which might have survival value for the organism.

The hypothesis is further strengthened by recent data from a microarray analysis of 8,435 genes in the left ventricular myocardium of rats [25]. There was a very significant similarity in expression profiles between hypothyroid and amiodarone-treated rats ($R = 0.63$, $P < 0.00001$); the correlation became even stronger when the top 100 up-regulated and 100 down-regulated genes in hypothyroidism were analyzed ($R = 0.78$, $P < 0.00001$).

As a final remark, however, it should be mentioned that not all pharmacological actions of amiodarone can be explained from the induction of a local hypothyroid-like condition in the heart. Evaluating the complete ion channel repertoire by real time PCR in hearts of mice treated with amiodarone, it became obvious that changes in transcript levels sometimes were similar to those seen in hypothyroid mice, but very frequently were completely different from the hypothyroid phenotype [26, 27]. Nevertheless, down-regulation of the effect of thyroid hormone in the heart results in what has been called “cardiac metamorphosis” [28], which by decreasing energy demands and increasing energy availability might be advantageous with potential therapeutic implications.

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